REMARKS

Claims 15-34 are pending in the present application. Each of the Examiner's rejections are addressed below.

Double Patenting

Claims 15-34 were rejected under the judicially created doctrine of obviousness-type double patenting, as allegedly being unpatentable over claims 1-12 of U.S. Patent No. 6,074,666. Applicants thank the Examiner for maintaining the rejection in abeyance pending a notification of allowable claims.

Rejection under 35 U.S.C. §102(e)

Claims 15-20 and 30-34 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Madden (U.S. Patent No. 5,389,378). The Examiner states that Madden discloses freeze-dried benzoporphyrins encapsulated in liposomes and containing lactose. Furthermore, the Examiner alleges that the liposomes described in Madden have the same osmolarity as blood because of its administration as an isotonic solution. See, Office Action mailed February 10, 2003, at page 4. Applicants must respectfully disagree.

A claim is anticipated only if each and every element as set forth in the claim is found in the prior art. Contrary to the Examiner's assertions, the liposomes of the presently claimed invention and the freeze-dried liposomes of Madden do not have the same osmolarities. Osmolarity is defined as the "osmotic concentration of a solution expressed as osmoles of solute per liter of solution." The American Heritage Stedman's Medical Dictionary, Houghton Mifflin Company 2001 (attached at Tab 1). Different methods for computing osmolarity are described in Remington: The Science and Practice of Pharmacy, attached at Tab 2. One method involves the calculation of osmolarity from the weight/volume concentration of the solutes in solution using the following

equation: (g/L x mols/g x osmol/mol x 1000 mOsmol/osmol = mOsmol/L). Thus, the osmolarity of a solution is necessarily affected by the total amount of solutes in solution.

In the presently claimed invention, the porphyrin-containing liposomes were dispersed in a dilute aqueous sugar solution and homogenized. In one example, the porphyrin-containing liposomes were dispersed in 10 % aqueous sugar solution. See Specification at Example 1. The liposomal formulations have the osmolarity of blood (about 300 mOsm /L), which may simply be reconstituted with water for injection. See claim 16 and Example 1.

Unlike the presently claimed invention, the freeze-dried porphyrin-containing liposomes in Madden were prepared in 250 mM lactose, 50 mM mannitol, 100 mM NaCl, and 20 mM citrate at pH 6.0. See Madden at Example 1. Based on the equation above for calculating osmolarity, with one mole of sodium chloride representing two osmoles of sodium chloride, the solution prepared in Madden has an osmolarity of 520 mOsmol/L (250 mOsmol/L + 50 mOsmol/L + 200 mOsmol/L + 20 mOsmol/L). Thus, the liposomes prepared in Madden do not have the osmolarity of blood, and do not anticipate the presently claimed invention.

However, the Examiner alleges that the liposomes described in Madden have the same osmolarity as blood because of its administration as an isotonic solution. Contrary to the Examiner's assertions, tonicity and osmolarity are distinct concepts. As previously indicated, osmolarity relates to the total concentration of solutes in a solution, regardless of whether the solutes can cross cell membranes or not. On the other hand, tonicity depends only on the relative concentrations of nonpenetrating solutes (i.e., particles that cannot cross the cell membrane) in the solution and in the cell. In calculating tonicity, the presence of penetrating solutes (i.e., solute particles that can enter the cell) is ignored since these solutes move freely into the cell, as if the cell membrane did not exist.

Tonicity describes what happens to cell volume if the cell is placed in a solution, and says nothing about the osmolarity of the solution. Specifically, tonicity is a relative comparison of one solution to another in which the first solution is hypertonic, hypotonic or isotonic to the second solution. If a solution has a high concentration of nonpenetrating solutes, water moves into the cell causing the cell to swell, and the solution is hypotonic. If the cell has a lower concentration of nonpenetrating solutes, water moves out of the cell, and the solution is hypertonic. If the concentrations of nonpenetrating solutions are the same in the cell and solution, there will be no net movement of water, and the solution is isotonic. In other words, the term "isotonic" refers to solutions in which cells neither swell nor shrink. See, Stedman's Medical Dictionary 26th Edition, attached at Tab 3.

To support the Examiner's rejection of Applicants' arguments that tonicity and osmolarity are distinct concepts, the Examiner has cited two references. The Examiner cites U.S. Patent No. 6,265,387 by Wolff, which states that "isotonic" means that the tonicity of the solution is similar to that of blood). See Wolff at column 7, lines 40-43. The Examiner also cites U.S. Patent No. 6,207,456 by Baru at column 3, lines 53-58, which mentions "isotonicity with body fluids."

Applicants respectfully assert that the Examiner has misinterpreted Wolff and Baru. As previously defined, isotonicity is distinct from osmolarity. Isotonicity of solutions with blood says nothing about the osmolarity of the solution because tonicity depends only on the concentrations of nonpenetrating solutes while osmolarity depends upon the total number of solutes in solution. A solution that is isotonic to blood only indicates that the solution will not cause blood cells to swell or shrink. On the other hand, hypertonic solutions have increased tonicity and cause cells to shrink. See Wolff at column 7, lines 41-45.

Because Madden is silent with regard to liposomes having an osmolarity of human blood, this patent does not anticipate claims 15-20 and 30-34. If the Examiner is relying upon the

theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. MPEP 2112 (quoting *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)). Based on the above, Applicants respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. §103(a)

Claims 26-27 and 33-34 were rejected under 35 U.S. C. § 103(a) as allegedly being unpatentable over Madden (U.S. Patent No. 5,389,378). The Examiner admits that Madden does not disclose the amounts of sugar in all of the claimed ratios. Office Action, page 4. However, the Examiner states that in view of Madden's teachings of the isotonic nature of the composition, "it is deemed obvious to manipulate the amounts of sugars and still achieve the isotonic nature of the composition as taught by Madden." Office Action, page 4. Applicants must respectfully disagree.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success should the modification or combination be carried out. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP 2143. As shown below, these requirements have not been met.

There is no suggestion or motivation to modify Madden such that the liposomes in Madden would have the osmolarity of blood. As previously indicated, the isotonic solutions in Madden say nothing about the osmolarity of the liposomes. Furthermore, Madden teaches the use of sugars merely as protective groups required for the dehydration process so that they can interact with the surfaces of the liposome membranes. See Madden at column 9, lines 8-30. More

importantly, Madden teaches that the use of sugars may be **omitted**. Specifically, sugars may be omitted if the liposomes being dehydrated have multiple lipid layers and the dehydration is carried out to an end point where there is sufficient water left in the preparation, so that a substantial portion of the membranes retain their integrity upon rehydration. See Madden at column 9, lines 31-37.

In contrast, the presently claimed invention teaches the use of sugars to obtain liposomes having the osmolarity of blood. For example, no more than 4-5 % monosaccharides can be added to keep the osmotic pressure of the liposome formulation similar to blood. Similarly, 9-10 % disaccharides can be added to obtain liposomes having the osmolarity of blood. See Specification at page 10, lines 4-8.

Because Madden teaches that sugars can be omitted in its liposomes, Madden **teaches away** from the presently claimed invention. Thus, it cannot have been obvious to adjust the amounts of sugar needed for liposome compositions having an osmolarity similar to blood. Applicants therefore respectfully request that this rejection be withdrawn.

Claims 28-29 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Madden, further in view of Barenholz (U.S. Patent No. 4,797,285). Office Action, page 5. The Examiner admits that Madden does not teach the inclusion of an antioxidant such as BHT. However, the Examiner states that the inclusion of a free-radical scavenger such as BHT in Madden would have been obvious since such an inclusion would prevent the oxidation of active agents as taught by Barenholz. Office Action, page 5. Applicants must respectfully disagree.

As previously indicated, there is no suggestion or motivation to modify Madden such that the liposomes in Madden would have the osmolarity of blood because isotonicity is distinct from osmolarity. Furthermore, even if Madden and Barenholz were combined, there is no reasonable expectation of success that the combination would result in the presently claimed

invention. Barenholz merely describes liposomes comprising an aqueous suspension of liposomes and an anthraquinone. Thus, the combination would only teach the use of antioxidants in liposomal formulations. Finally, even if Madden and Barenholz were combined, the combination does not teach all the elements of the presently claimed invention because neither reference teaches liposomes having the osmolarity of blood. Applicants therefore respectfully request that this rejection be withdrawn.

Claims 20-25 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Madden. The Examiner states that the use of known porphyrin derivatives with the expectation of obtaining "similar results" would have been obvious. Applicants must respectfully disagree. Specifically, because Madden fails to teach liposomes having the osmolarity of blood, Madden could not have rendered the claims obvious. Thus, Applicants respectfully request that this rejection be withdrawn.

Claims 15-20 and 25-34 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Thompson (U.S. Patent No. 5,277,913) or Kappas (U.S. Patent No. 5,010,073) in view of Crowe (U.S. Patent 4,857,319), further in view of Madden. The Examiner admits that Thompson and Kappas do not teach the presence of sugars. Office Action, page 6. The Examiner also admits that these references do not teach compositions having the osmolarity of blood. Office Action, page 6. However, the Examiner states that the use of sugars in the liposomes of Thompson and Kappas would have been obvious since sugars preserve liposomes during dehydration and rehydration. The Examiner also alleges that the addition of sugars would be obvious since these compounds are helpful in making the compositions isotonic as taught by Madden. Applicants must respectfully disagree.

First, there is no suggestion or motivation to modify or combine Thompson or Kappas, in view of Crowe and Madden. Thompson and Kappas teach liposomal porphyrins and photodynamic

therapy. Crowe teaches that sugars protect liposomes during dehydration and rehydration. As previously indicated, Madden also teach the addition of sugars during dehydration and rehydration. However, Madden teaches that sugars may be omitted in certain liposomal compositions that retain their integrity upon rehydration. See Madden at column 9, lines 31-37. Where the reference teaches away from their combination, the references cannot be combined. MPEP 2146 (citing *In re Grasselli*, 713 F.2d 731, 743, 219 USPQ 769, 779 (Fed. Cir. 1983)).

Second, even if the references were combined, there is no a reasonable expectation of success that the combination would result in the presently claimed invention. Specifically, none of these references suggest that sugars can be used to obtain liposomes having the osmolarity of blood. As previously indicated, Madden teaches the omission of sugars, and Crowe only teaches the use of sugars as protective groups. Furthermore, as the Examiner admits, Thompson and Kappas do not teach the presence of sugars. Thus, the combination would only teach the use of sugars as protective groups in liposome formulations. Finally, even if the references were combined, the combination does not teach all the elements of the presently claimed invention because none of the references teach liposomes having the osmolarity of blood. Applicants therefore respectfully request that this rejection be withdrawn.

Claims 28-29 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Thompson or Kappas in view of Crowe and Madden, and further in view of Barenholz. The Examiner admits that Thompson, Kappas, Crowe and Madden do not teach the inclusion of an antioxidant such as BHT. Office Action, page 7. However, the Examiner states that it would have been obvious to include a free-radical scavenger such as BHT to prevent the oxidation of active agents as taught by Barenholz. Applicants must respectfully disagree.

As previously indicated, the references may not be combined since Madden teaches away from the combination. Furthermore, there is no a reasonable expectation of success that the

combination would result in the presently claimed invention. The combination would only teach the use of antioxidants in liposome formulations. Further, even if combined, the combination does not teach liposomes having the osmolarity of blood because none of the references teach liposomes having the osmolarity of blood. Applicants therefore respectfully request that this rejection be withdrawn.

Claims 20-25 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Madden, Thompson or Kappas, in view of Crowe. The Examiner admits that neither Madden, Thompson nor Kappas teach all the porphyrin derivatives in the instant claims. Office Action, page 8. However, the Examiner asserts that the use of known porphyrin derivatives in the liposomes of Madden, Thompson or Kappas with the expectation of obtaining liposomes having an osmolarity of blood would have been obvious. Applicants must respectfully disagree.

As the Examiner admits, neither Madden, Thompson nor Kappas teach all the porphyrin derivates in the instant claims. As previously indicated, there is no motivation to combine the references because Madden teaches away from the combination. Furthermore, there is no a reasonable expectation of success that the combination would result in the presently claimed invention. The combination would only teach the use of sugars as protective groups in liposome formulations. Further, even if combined, the combination does not teach liposomes having the osmolarity of blood because none of the references teach liposomes having the osmolarity of blood. Applicants therefore respectfully request that this rejection be withdrawn.

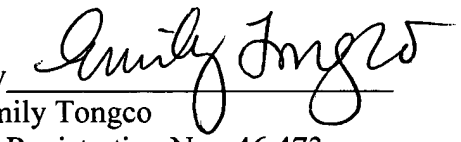
CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant(s) petition(s) for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 273012008102.

Dated: September 25, 2003

Respectfully submitted,

By 

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